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Efficient synthesis of trifluoro- and difluoroacetyl hydrazides as useful building blocks for non-symmetrically substituted, fluorinated 1,3,4-oxadiazoles

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Abstract

A convenient and efficient approach to 2-arylamino-5-fluoroalkyl-1,3,4-oxadiazoles has been established via heterocyclization of corresponding di- and trifluoroacetylated thiosemicarbazides by treatment with dicyclohexylcarbodiimide (DCC). Another heterocyclization performed with selected thiosemicarbazides under basic conditions led to 4-aryl-5-fluoroalkyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones in moderate yields. As a precondition for these transformations, a smooth preparation of the fluoroacetylated thiosemicarbazides via fluoroacetylation of benzyloxycarbonyl (Cbz)-protected hydrazine with a corresponding anhydride, followed by hydrogenolytic deprotection and reaction with arylisothiocyanates has been elaborated. Similarly, fluoroacetylated semicarbazides were prepared, but all attempts to achieve their heterocyclization were unsuccessful.

1. Introduction

Fluorinated heterocycles are widely applied as biologically active compounds for the preparation of new drugs, agrochemicals and materials with special properties [1]. The development of methods for stereoselective syntheses of diverse fluorinated N-heterocycles is also of current interest [2]. Among heterocyclic systems which attract great attention, an important class comprises 1,3,4-oxadiazole derivatives [3] including fluorinated examples [4].

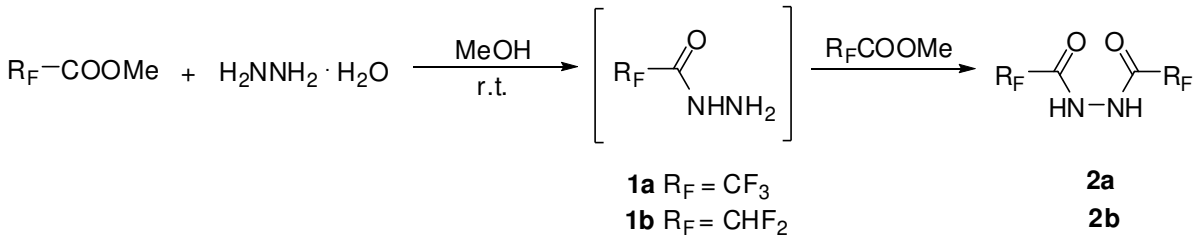
Hydrazides of carboxylic acids (carbohydrazides) are known as versatile building blocks used for the preparation of heterocyclic compounds with diverse ring size. Target heterocycles can be synthesized starting either with substituted carbohydrazides or their derivatives such as hydrazones, semicarbazides, thiosemicarbazides, etc. [5]. A known method for the preparation of 1,3,4-oxadiazoles is the treatment of semicarbazides derived from carbohydrazides with sulfuric acid [6] or another acidic agent. Alternatively, they can be obtained directly from carbohydrazides via the reaction with orthoesters [7].

Due to our continuing interest in the development of methods for the synthesis of fluorinated heterocycles [8], we focused attention on the exploration of the relatively little known trifluoro- and difluoroacetyl hydrazides (**1a**, **b)** as potential precursors for the preparation of fluorinated 1,3,4-oxadiazoles. The method selected for the synthesis of the latter was heterocyclization of semicarbazides of fluorinated carbohydrazides using sulfuric acid. In addition, analogous heterocyclizations should be performed starting with thiosemicarbazides and selenosemicarbazides in order to obtain the corresponding 1,3,4-thia- or 1,3,4-selenadiazoles.

2. Results and discussion

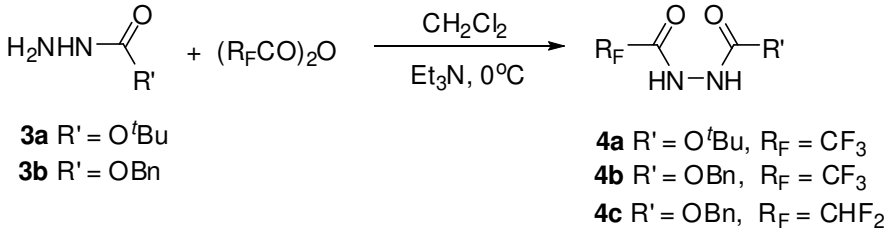
Typically, the access to carbohydrazides is based on the reaction of the corresponding carboxylic esters with an equimolar amount of hydrazine hydrate [5]. In our hands, treatment of methyl trifluoroacetate with 1–5.0 equivalents of hydrazine hydrate in methanolic solution led to bis(trifluoroacetyl)hydrazine (**2a**) as the product (Scheme 1). Its structure was confirmed by the ESI-MS registered for the crude product, which displayed a single signal for *m/z* 223.2. Increasing of the amount of hydrazine hydrate to 1:10 or 1:20 resulted in a mixture of comparable amounts of **2a** and **1a** or in the exclusive formation of **1a**, respectively. Apparently, the initially formed **1a** reacts

rapidly with the starting ester yielding **2a** as the final product. The formation of the analogous product **2b** was observed using methyl difluoroacetate in the reaction with hydrazine hydrate. In the course of the attempted synthesis of **1a**, the tested protocol with 20-fold excess of hydrazine hydrate was practically useless as the expected product could not be efficiently separated from the excess of hydrazine hydrate. In the light of the presented results, the reported syntheses of **1a** from trifluoroacetates and hydrazine hydrate used in nearly equimolar amounts seem to be non-reproducible protocols [9]. However, instability of **1a** was observed during the storage of the isolated product already at room temperature [9a].



Scheme 1

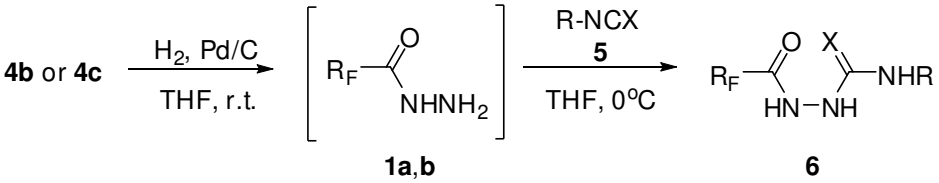
For that reason, the Boc- and Cbz-protected hydrazines **3a** and **3b**, respectively, were prepared and converted into the *N*-protected non-symmetrical trifluoro- and difluoroacetyl hydrazines **4a**–**4c** by treatment with trifluoro- or difluoroacetic anhydride (Scheme 2). Similar approaches for the synthesis of **1a** based on the application of *N*-Boc protected hydrazine were only rarely reported [10].



Scheme 2

However, in our hands, the attempted deprotection of the Boc-hydrazide **4a** performed typically by treatment with trifluoroacetic acid in CH_2Cl_2 at 0 ºC or with HCl in dioxane at 0 ºC yielded exclusively the symmetrical **2a**. On the other hand, hydrogenolysis of **4b** and **4c** over Pd/C in THF at room temperature afforded the desired trifluoro- and

difluoroacetyl hydrazides **1a** and **1b**, respectively, as sole products (Scheme 3). In the case of **1a**, the attempted isolation led again to its conversion into the symmetrical **2a**. Therefore, freshly prepared **1a** and **1b** in THF solution were treated with isocyanates, isothiocyanates and isoselenocyanates **5** (X = O, S, Se, resp., Scheme 3). The most reactive isocyanates **5** (X = O) formed the expected semicarbazides **6a**–**f** (X = O) in high yields (Scheme 3, Table 1). Similarly, aromatic isothiocyanates **5** (X = S) gave thiosemicarbazides **6g**–**j** (X = S) in good yields, and only in the case of the less reactive cyclohexylisothiocyanate the corresponding products **6k** and **6l** (X = S) were formed in low yields and could not be isolated in pure form. Finally, the attempted reactions of **1a**,**b** with phenyl isoselenocyanate led to black colored, complex mixtures of non-identified products.



Scheme 3

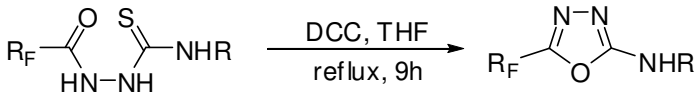
Table 1. Prepared *N*-acylated semicarbazides and thiosemicarbazides **6**.

Hydrazide	R_F	Reagent	R	X	Product	Yield (%)[a]
1a	CF_3	**5a**	Ph	O	**6a**	88
1a	CF_3	**5b**	4-FC_6H_4	O	**6b**	91
1a	CF_3	**5c**	4-$MeOC_6H_4$	O	**6c**	86
1a	CF_3	**5d**	*c*Hex	O	**6d**	93
1b	CHF_2	**5a**	Ph	O	**6e**	90
1b	CHF_2	**5d**	*c*Hex	O	**6f**	94
1a	CF_3	**5e**	Ph	S	**6g**	77
1a	CF_3	**5f**	4-FC_6H_4	S	**6h**	74
1a	CF_3	**5g**	4-$MeOC_6H_4$	S	**6i**	68
1b	CHF_2	**5e**	Ph	S	**6j**	80
1a	CF_3	**5h**	*c*Hex	S	**6k**	ca. 30[b]
1b	CHF_2	**5h**	*c*Hex	S	**6l**	ca. 30[b]

[a] Yields of isolated products.

[b] Symmetrical *N,N'*-bis(trifluoroacetyl)hydrazine (**2a**) was formed as a by-product and separation of the mixture could not be achieved. Yields of **6k** and **6l** were estimated based on the registered MS spectra.

First experiments aimed at the preparation of fluorinated 1,3,4-oxadiazoles were performed with **6a** using ethyl orthoacetate and catalytic amounts of *p*-TsOH, but in this case a complex mixture of non-identified products was formed. Similarly, treatment of **6a** with conc. H_2SO_4 led to the same result. Finally, the reaction of thiosemicarbazides **6g–j** with DCC in boiling THF afforded selectively 2-amino-1,3,4-oxadiazoles **7a–d** in excellent yields (Scheme 4, Table 2). Analytically pure products were isolated after flash column chromatography. Their structures were established by means of spectroscopic methods. For example, the ^{13}C-NMR spectrum of **7a** revealed a singlet for C(2) at 161.7 ppm and a quartet for C(5) with $^2J_{C,F}$ = 42.9 Hz at 147.9 ppm. The characteristic quartet with $^1J_{C,F}$ = 268.1 Hz at 116.8 ppm was attributed to the CF_3 group. In addition, the ^{19}F-NMR spectrum showed the signal of the CF_3 group at –64.6ppm.



6g-j **7a-d**

Scheme 4

Table 2. Synthesis of fluorinated 2-amino-1,3,4-oxadiazoles **7** via heterocyclization of acylated thiosemicarbazides **6**.

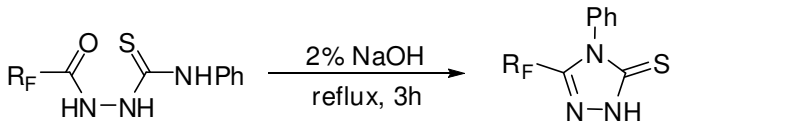
Thiosemicarbazide	R_F	R	1,3,4-Oxadiazole	Yield (%)[a]
6g	CF_3	Ph	**7a**	92
6h	CF_3	4-FC_6H_4	**7b**	95
6i	CF_3	4-$MeOC_6H_4$	**7c**	80
6j	CHF_2	Ph	**7d**	82

[a] Yield of isolated product.

It is worth mentioning that an efficient access to 2-amino-1,3,4-oxadiazoles comprises the reaction of thiosemicarbazides of type **6** (X = S) with TsCl and pyridine [11]. In

some cases, the same product could be obtained from the corresponding semicarbazide, albeit in significantly lower yield and after longer reaction time. The reported formation of **7a** as the exclusive product was confirmed also in our laboratory.

In extension of the study, fluorinated thiosemicarbazides **6g** and **6j** were heated in a aqueous solution of NaOH (2%) and 1,2,4-triazole-3-thiones **8** were obtained in moderate yields (Scheme 5). This observation confirms the behavior of thiosemicarbazides under basic conditions [12]. Again, the attempted cyclization of corresponding semicarbazides **6** (X = O) under analogous conditions was unsuccessful.



6g $R_F = CF_3$
6j $R_F = CHF_2$

8a $R_F = CF_3$ (34%)
8b $R_F = CHF_2$ (36%)

Scheme 5

3. Conclusions

The present study showed that in addition to other methods for the preparation of 2-amino-1,3,4-oxadiazoles based on the heterocyclization of semicarbazides, the corresponding thiosemicarbazides can also be used including fluorinated derivatives. The heterocyclization of fluorinated thiosemicarbazides can be efficiently performed using DCC as the activating and H_2S-binding reagent. This protocol supplements the already reported method with *p*-TsCl and pyridine in THF solution [11]. In both procedures, the heterocyclization occurs chemoselectively via the conversion of the more nucleophilic C=S function into a good leaving group and the subsequent nucleophilic attack of the O-atom leading to 2-amino-1,3,4-oxadiazoles as final products. This type of chemoselectivity is preserved also in thiosemicarbazides containing an electron-deficient R_FCO group. Another method for the synthesis of symmetrical 2,5-bis(perfluoroalkyl)-substituted 1,3,4-oxadiazoles from 1,2-diacylhydrazines, prepared stepwise by two-fold acylation of hydrazine, is the cyclization by treatment with $POCl_3$ as activating and dehydrating agent [9b]. This approach can be considered as a pioneering method for the synthesis of 1,3,4-oxadiazoles [13].

The presented method for the preparation of fluorinated 2-amino-1,3,4-oxadiazoles requires an efficient access to fluorinated monoacetylhydrazines. Our study showed that they can be synthesized from Cbz-protected hydrazine and the corresponding fluorinated acetanhydrides. After the deprotection, the obtained carbohydrazides have to be reacted immediately with isocyanates or isothiocyanates to give the required semicarbazides and thiosemicarbazides, respectively. Otherwise they undergo spontaneous disproportionation yielding symmetrical 1,2-diacylhydrazines, which are of limited importance for further applications.

4. Experimental

4.1. General information

Melting points were determined on a Melt-Temp II apparatus (Aldrich) in capillaries, and they are uncorrected. The ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded on a Bruker Avance III 600 spectrometer using the solvent signal as reference. Assignments of signals in ^{13}C NMR spectra were achieved using HMQC and HMBC techniques. IR spectra were measured using a NEXUS FT-IR spectrophotometer. The ESI-MS spectra were obtained using a Varian 500 MS LS Ion Trap spectrometer. Elemental analyses were recorded on Elementar Vario Micro Cube apparatus.

4.2. Materials

All solvents were used as commercial products. Methyl trifluoroacetate, methyl difluoroacetate, trifluoroacetic acid anhydride, and difluoroacetic acid anhydride, were purchased from Fluorochem. Chloroform was dried over phosphorus pentoxide (P_2O_5) and freshly distilled prior to use. Tetrahydrofuran (THF) was dried over sodium in the presence of benzophenone and freshly distilled from the violet-colored solution prior to use. Anhydrous ethanol was dried over calcium oxide and CH_2Cl_2 over calcium hydride. (*tert*-Butoxycarbonyl)hydrazine (**3a**) [14a] and (benzyloxycarbonyl)hydrazine (**3b**) [14b] were obtained according to the known protocols.

4.3. Synthesis of the symmetrical N,N'*-bis(trifluoroacetyl)hydrazine (**2a**).*

Ethyl trifluoroacetate (142 mg, 1.0 mmol) was added dropwise to the solution of hydrazine hydrate (50 mg, 1.0 mmol) in MeOH (~5.0 ml). The reaction mixture was stirred over 1 h at room temperature. Next, the solvent was evaporated and the solid product was crystallized from EtOH.

N,N'-*Bis(trifluoroacetyl)hydrazine* (**2a**): Yield 160 mg (71%), m.p. = 173–175 °C (EtOH), (lit. [9b], m.p. 176 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.45 (br.s, 2H, 2 NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 118.1 (q, $^{1}J_{C,F}$ = 284.4 Hz, 2 CF_3), 159.1 (q, $^{2}J_{C,F}$ = 31.0 Hz, 2 C=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –72.9 (s, 6F, 2 CF_3). IR (KBr): *v* 3346*m*, 3293*w*, 3213*w*, 3142*w*, 2989*m*, 2957*w*, 2858*w*, 2756*w*, 1612*vs*, 1520*w*, 1414*m*, 1203*vs*, 1190*vs*, 1146*vs*, 1098*s*, 973*m* cm^{-1}. HR-EI-MS: calcd. for $C_4H_2F_3N_2O_2^+$ (M^+): *m*/*z* 224.00205; found: *m*/*z* 224.00128.

*4.4. Reactions of protected hydrazines **3a**,**b** with fluorinated acids anhydrides – General procedure*

A solution of $BocNHNH_2$ (**3a**, 3.0 mmol, 498 mg) or $CbzNHNH_2$ (**3b**, 3.0 mmol, 396 mg) in anhydrous CH_2Cl_2 (~30 ml) was placed in an ice-bath (~0 °C). Next, triethylamine (4.5 mmol, 455 mg) was added, and after ca. 20 min, the appropriate fluorinated anhydride (3.2 mmol) was added dropwise while cooling the reaction flask in an ice-bath. The reaction mixture was stirred at room temperature for 2 h. Then, the solvent was evaporated and crude products were purified by column chromatography (SiO_2, hexane/ethyl acetate, 1:1). Analytically pure samples were obtained after crystallization from an appropriate solvent.

4.4.1. N-*Trifluoroacetyl*-N'-*(*tert-*butoxycarbonyl)hydrazine* (**4a**). Yield: 608 mg (89%), colorless crystals, m.p. 129–131 °C (Et_2O/hexane), (lit. [10a], m.p. = 130–132 °C). ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.43 (s, 9H, 3 CH_3), 9.28 (s, 1H, NH), 11.23 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 28.4 (3 CH_3), 80.6 (**C**$(CH_3)_3$), 116.3 (q, $^{1}J_{C,F}$ = 286.5 Hz, CF_3), 154.9 (C=O), 156.7 (q, $^{2}J_{C,F}$ = 35.1 Hz, CF_3**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –74.0 (s, 3F, CF_3). IR (KBr): *v* 3294*s*, 3196*m*, 3031*m*, 3000*m*, 2989*m*, 2914*w*, 1741*s*, 1690*vs*, 1571*w*, 1506*s*, 1457*w*, 1400*w*, 1369*m*, 1247*s*, 1207*vs*, 1162*s*, 1137*s*, 1052*w*, 1024*w*, 901*w*, 857*w*, 732*m*, 675*w* cm^{-1}. ESI-(–)-MS: *m*/*z* 227 (100%,

[M–1]$^-$). Anal. calcd for $C_7H_{11}F_3N_2O_3$: C, 36.85; H, 4.86; N, 12.28; found: C, 37.02; H, 4.96; N, 12.30.

4.4.2. N-*Trifluoroacetyl-N'-(benzyloxycarbonyl)hydrazine* (**4b**). Yield: 605 mg (77%), colorless crystals, m.p. 109–111 °C (Et_2O/hexane). ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.14 (s, 2H, CH_2), 7.35–7.39 (m, 5 arom. CH), 9.75 (br. s, 1H, NH), 11.44 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 66.9 (CH_2), 116.3 (q, $^1J_{C,F}$ = 286.5 Hz, CF_3), 128.4, 128.6, 128.9 (5 arom. CH), 136.7 (1 arom. C), 155.8 (C=O), 156.7 (q, $^2J_{C,F}$ = 35.8 Hz, CF_3**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –74.0 (s, 3F, CF_3). IR (KBr): *ν* 3335*m*, 3268*m*, 3227*m*, 3041*m*, 2968*w*, 2915*w*, 1761*s*, 1713*s*, 1689*s*, 1549*m*, 1511*m*, 1357*w*, 1243*vs*, 1209*vs*, 1158*s*, 1046*w*, 969*w*, 746*m*, 697*m* cm^{-1}. ESI-(–)-MS: *m/z* 261 (100%, [M–1]$^-$). Anal. calcd for $C_{10}H_9F_3N_2O_3$: C, 45.81; H, 3.46; N, 10.68; found: C, 45.67; H, 3.56; N, 10.85.

4.4.3. N-*Difluoroacetyl*-N'-*(benzyloxycarbonyl)hydrazine* (**4c**). Yield: 682 mg (93%), colorless crystals, m.p. 116–117 °C (Et_2O/hexane). ^{1}H NMR (600 MHz, DMSO-d_6): δ 5.13 (s, 2H, CH_2), 6.37 (t, $^2J_{H,F}$ = 52.9 Hz, 1H, CHF_2), 7.35–7.39 (m, 5 arom. CH), 9.51 (s, 1H, NH), 10.74 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 66.7 (CH_2), 108.6 (t, $^1J_{C,F}$ = 245.4 Hz, CHF_2), 128.4, 128.5, 128.9 (5 arom. CH), 136.9 (1 arom. C), 156.0 (C=O), 162.3 (t, $^2J_{C,F}$ = 25.0 Hz, CHF_2**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –126.8 (d, $^2J_{H,F}$ = 52.9 Hz, 2F, CHF_2). IR (KBr): *ν* 3316*m*, 3091*w*, 3064*w*, 3040*w*, 3017*w*, 2996*w*, 2965*w*, 2903*w*, 1739*m*, 1683*m*, 1546*m*, 1506*m*, 1464*w*, 1384*w*, 1358*w*, 1257*m*, 1205*w*, 1106*w*, 1056*m*, 960*w*, 750*m*, 701*m*, 580*m* cm^{-1}. ESI-(+)-MS: *m/z* 267 (100%, [M+23]$^+$), ESI-(–)-MS: m/z 243 (100%, [M–1]$^-$). Anal. calcd for $C_{10}H_{10}F_2N_2O_3$: C, 49.19; H, 4.13; N, 11.47; found: C, 49.32; H, 4.13; N, 11.60.

4.5. Preparation of fluorinated acid hydrazides via hydrogenolysis of N-*difluoroacetyl-and* N-*trifluoroacetyl*-N'-*(benzyloxycarbonyl)hydrazines and their reactions with isocyanates and isothiocyanates – General procedure*

A portion of the catalyst (10% Pd/C (60 mg)) was added to the solution of the CBz-protected hydrazide (**6a** or **6b**; 2.0 mmol) in anhydrous THF (~50 ml). Next, the reaction flask was equipped with a septum, a long syringe and a balloon filled with hydrogen. Progress of the reaction was monitored by TLC (SiO_2, hexane/AcOEt 1:1),

and as soon as the reaction was finished, the solution was filtered through a Celite pad. Next, the appropriate isocyanate **5a**–**d** or isothiocyanate **5e**–**h** (2.2 mmol), was added dropwise to the filtrate while cooling the reaction flask in the ice-bath (~0^{o} C). The mixture was stirred overnight at room temperature. After evaporation of the solvent, crude products were purified by column chromatography (SiO_2, hexane with increasing amount of AcOEt 40–90%). Semicarbazides **6a**–**f** and thiosemicarbazides **6g**–**j** were obtained as amorphous solids by trituration with Et_2O.

4.5.1. N-*Phenyl trifluoroacetic acid semicarbazide* (**6a**). Yield: 436 mg (88%), colorless crystals, m.p. 176–178 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.98–7.00 (m, 1 arom. CH), 7.26–7.29 (m, 2 arom. CH), 7.45–7.46 (m, 2 arom. CH), 8.44 (br. s, 1H, NH), 8.96 (br. s, 1H, NH), 11.24 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 116.5 (q, $^{1}J_{C,F}$ = 289.4 Hz, CF_3), 119.1, 122.7, 129.1 (5 arom. CH), 139.8 (1 arom. C–NH), 154.7 (C=O), 156.8 (q, $^{2}J_{C,F}$ = 34.8 Hz, CF_3**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –73. 6 (s, 3F, C**F**$_3$). IR (KBr): *v* 3297*s*, 3057*m*, 2890*w*, 1727*vs*, 1667*vs*, 1608*s*, 1574*s*, 1558*m*, 1360*m*, 1317*m*, 1303*m*, 1216*s*, 1189*vs*, 1165*vs*, 1128*s*, 1078*w*, 1044*w*, 1033*w*, 920*m*, 857*w*, 745*m*, 695*m*, 633*m*, 581*w* cm^{-1}. ESI-(+)-MS: *m/z* 248 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 246 (100%, $[M–1]^-$). HR-EI-MS: calcd. for $C_9H_8F_3N_3O_2^+$ (M^+): *m/z* 247.05686; found: *m/z* 247.05713.

4.5.2. N-*(4-Fluorophenyl) trifluoroacetic acid semicarbazide* (**6b**). Yield*:* 483 mg (91%), colorless crystals, m.p. = 190–191 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.10–7.13 (m, 2 arom. CH), 7.45–7.48 (m, 2 arom. CH), 8.49 (br. s, 1H, NH), 9.04 (br. s, 1H, NH), 11.23 (br. s 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 115.6, 115.7 (4 arom. CH), 116.4 (q, $^{1}J_{C,F}$ = 286.6 Hz, CF_3), 136.1 (1 arom. C–NH), 154.8 (C=O), 157.1 (q, $^{2}J_{C,F}$ = 35.7 Hz, F_3C**C**=O), 158.0 (d, $^{1}J_{C,F}$ = 237 Hz, 1 arom. C–F) ppm. ^{19}F NMR (565 MHz, DMSO-d_6): δ –117.3 (s, 1F, CF), –73.7 (s, 3F, CF_3). IR (KBr): *v* 3378*m*, 3319*m*, 3265*m*, 3227*m*, 3065*w*, 2908*w*, 1720*m*, 1690*s*, 1664*s*, 1620*w*, 1571*s*, 1514*s*, 1411*w*, 1363*w*, 1277*w*, 1219*s*, 1198*s*, 1170*s*, 1124*w*, 1099*w*, 1053*w*, 1015*w*, 923*w*, 832*w*, 793*w*, 739*w*, 635*w* cm^{-1}. ESI-(+)-MS: *m/z* 266 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 264 (100%, $[M–1]^-$). HR-EI-MS: calcd. for $C_9H_7F_4N_3O_2^+$ (M^+): *m/z* 265.04744; found: *m/z* 265.04734.

4.5.3. N-*(4-Methoxyphenyl) trifluoroacetic acid semicarbazide* (**6c**). Yield: 475 mg (86%), colorless crystals, m.p. = 186–188 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.72 (s, 3H, CH_3), 6.85–6.88 (m, 2 arom. CH), 7.33–7.36 (m, 2 arom. CH), 8.36 (br. s, 1H, NH), 8.79 (br. s, 1H, NH), 11.18 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 55.6 (OCH_3), 114.4, 114.5, 120.4, 121.1 (4 arom. CH), 116.4 (q, $^{1}J_{C,F}$ = 286.6 Hz, CF_3), 132.7 (1 arom. C–NH), 155.0 (1 arom. **C**–OCH_3), 155.2 (C=O), 157.0 (q, $^{2}J_{C,F}$ = 35.4 Hz, CF_3**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –73.7 (s, 3F, CF_3). IR (KBr): *ν* 3289*s*, 3146*w*, 3088*w*, 3056*w*, 3008*w*, 2954*w*, 2914*w*, 2837*w*, 1728*s*, 1668*vs*, 1608*s*, 1575*s*, 1540*m*, 1515*s*, 1465*w*, 144*w*, 1361*w*, 1304*w*, 1251*s*, 1218*s*, 1190*s*, 1173*vs*, 1128*s*, 1104*m*, 1031*m*, 920*m*, 836*m*, 799*w*, 836*m*, 739*m*, 636*m* cm^{-1}. ESI-(+)-MS: *m/z* 278 (75%, $[M+1]^+$), 300 (100%, $[M+23]^+$), ESI-(–)-MS: *m/z* 276 (100%, $[M-1]^-$). HR-EI-MS: calcd. for $C_{10}H_{10}F_3N_3O_3^+$ (M^+): *m/z* 277.06743; found: *m/z* 277.06731.

4.5.4. N-*Cyclohexyl trifluoroacetic acid semicarbazide* (**6d**). Yield: 471 mg (93%), colorless crystals, m.p. = 151–152 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.11–1.30, 1.54–1.76 (2m 10H, 5 CH_2), 3.39–3.40 (m, 1H, CH), 6.38 (br. s, 1H, NH), 7.99 (br. s, 1H, NH), 11.02 (s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.0, 25.6, 33.3 (5 CH_2), 48.8 (CH), 116.4 (q, $^{1}J_{C,F}$ = 286.5 Hz, CF_3), 156.5 (C=O), 156.9 (q, $^{2}J_{C,F}$ = 35.5 Hz, CF_3**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –73.7 (s, 3F, CF_3). IR (KBr): *ν* 3331*m*, 3267*m*, 3116*w*, 3027*w*, 2935*m*, 2858*m*, 1748*s*, 1737*m*, 1675*s*, 1636*m*, 1589*m*, 1551*w*, 1489*w*, 1465*w*, 1456*w*, 1358*w*, 1317*w*, 1253*m*, 1239*m*, 1204*s*, 1164*s*, 1133*m*, 1078*m*, 1018*w*, 914*w*, 891*w*, 795*w*, 737*m*, 656*w* cm^{-1}. ESI-(+)-MS: *m/z* 254 (25%, $[M+1]^+$), 276 (100%, $[M+23]^+$); ESI-(–)-MS: *m/z* 252 (100%, $[M-1]^-$). HR-EI-MS: calcd. for $C_9H_{14}F_3N_3O_2^+$ (M^+): *m/z* 253.10381; found: *m/z* 253.10283.

4.5.5. N-*Phenyl difluoroacetic acid semicarbazide* (**6e**). Yield: 410 mg (90%), colorless crystals, m.p. = 172–174 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.32 (t, $^{1}J_{C,F}$ = 52.1 Hz, CHF_2), 6.96–6.98 (m, 1 arom. CH), 7.25–7.27 (m, 2 arom. CH), 7.43–7.45 (m, 2 arom. CH), 8.39 (br. s, 1H, NH), 8.89 (br. s, 1H, NH), 10.64 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6):δ 108.4 (t, $^{1}J_{C,F}$ = 244.5 Hz, CHF_2), 118.8, 122.2, 128.8 (5 arom. CH), 139.0 (1 arom. C–NH), 154.7 (C=O), 161.9 (t, $^{2}J_{C,F}$= 25.2Hz, CHF_2**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ – 126.5 (d, $^{2}J_{F,H}$ = 52.1 Hz, 2F, CHF_2). IR (KBr): *ν* 3366*s*, 3300*s*, 3199*s*, 3099*m*, 3039*m*, 2926*w*, 2857*w*, 1946*w*, 1929*w*, 1739*s*, 1717*vs*, 1693*vs*, 1653*s*, 1600*vs*, 1564*s*, 1498*s*, 1444*s*, 1383*w*, 1320*m*, 1254*m*, 1218*m*, 1174*m*, 1151*w*,

1109*s*, 973*w*, 906*w*, 837*w*, 745*s*, 692*m*, 645*m* cm^{-1}. ESI-(+)-MS: *m/z* 252 (100%,$[M+23]^+$); ESI-(–)-MS: *m/z* 228 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_{15}F_2N_3O_2^+$ (M^+): *m/z* 229.06628; found: *m/z* 229.06638.

4.5.6. N-*Cyclohexyl difluoroacetic acid semicarbazide* (**6f**). Yield: 442 mg (94%), colorless crystals, m.p. =178–179 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.13–1.28, 1.65–1.76 (2m, 10H, 5 CH_2), 3.31–3.42 (m, CH), 6.26 (t, $^1J_{C,F}$ = 53.2 Hz, CHF_2), 6.28 (br. s, 1H, NH), 7.88 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.0, 25.7, 33.4 (5 CH_2), 48.6 (CH), 108.6 (t, $^1J_{C,F}$ = 244.2 Hz, CHF_2), 156. 8 (C=O), 162.0 (t, $^2J_{C,F}$ = 25.2 Hz, CHF_2**C**=O). ^{19}F NMR (565 MHz, DMSO-d_6): δ –126.5 (d, $^2J_{F,H}$ = 53.2 Hz, 2F, CHF_2). IR (KBr): *v* 3391*m*, 3351*s*, 3231*s*, 3104*w*, 3038*w*, 2935*s*, 2856*m*, 1731*s*, 1709*s*, 1656*vs*, 1564*vs*, 1464*w*, 1454*m*, 1399*w*, 1370*w*, 1346*w*, 1320*w*, 1277*w*, 1258*w*, 1238*m*, 1190*w*, 1125*s*, 1095*m*, 1076*m*, 978*w*, 967*w*, 893*w*, 845*w*, 824*w*, 773*w*, 670*w*, 639*w* cm^{-1}. ESI-(+)-MS: *m/z* 236 (50%, $[M+1]^+$), 258 (100%, $[M+23]^+$); ESI-(–)-MS: *m/z* 234 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_{15}F_2N_3O_2^+$ (M^+): *m/z* 235.11323; found: *m/z* 235.11329.

4.5.7. N-*Phenyl trifluoroacetic acid thiosemicarbazide* (**6g**). Yield: 405 mg (77%); colorless crystals, m.p. = 128–129 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.18–7.46 (m, 5 arom. CH), 9.75 (br. m, 2H, 2 NH), 11.52 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 116.8 (q, $^1J_{C,F}$ = 291.7 Hz, CF_3), 125.6 (1 arom. C–NH), 128.7, 139.4 (5 arom. CH), 155.8 (q, $^2J_{C,F}$ = 30.0 Hz, CF_3**C**=O), 179.9 (C=S). ^{19}F NMR (565 MHz, DMSO-d_6): δ –73.6 (s, 3F, CF_3). IR (KBr): *v* 3310*m*, 3158*m*, 3034*m*, 2891*w*, 1735*vs*, 1628*w*, 1594*m*, 1538*s*, 1520*s*, 1498*m*, 1487*m*, 1451*m*, 1418*w*, 1362*w*, 1270*w*, 1217*s*, 1166*vs*, 1155*vs*, 1117*m*, 1029*w*, 1005*w*, 935*w*, 898*w*, 745*m*, 697*m*, 638*w*, 615*w*, 526*m* cm^{-1}. ESI-(+)-MS: *m/z* 264 (75%, $[M+1]^+$), 286 (100%, $[M+23]^+$); ESI-(–)-MS: *m/z* 262 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_8F_3N_3OS^+$ (M^+): *m/z* 263.03402; found: *m/z* 263.03415.

4.5.8. N-*(4-Fluorophenyl) trifluoroacetic acid thiosemicarbazide* (**6h**). Yield: 415 mg (74%), colorless crystals, m.p. = 138–139 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.17–7.20 (m, 2 arom. CH), 7.45 (m, 2 arom. CH), 9.85 (br. m, 2H, 2 NH), 11.53 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 116.0, 115.5 (4 arom. CH), 116.9 (q, $^1J_{C,F}$ = 289.5 Hz, CF_3), 136.1 (1 arom. C–NH), 157.3 (q, $^2J_{C,F}$ = 35.7 Hz, F_3C**C**=O), 158.1 (d,

$^{1}J_{C,F}$ = 237.1 Hz, 1 arom. C–F) 178.1 (C=S) ppm. ^{19}F NMR (565 MHz, DMSO-d_6): δ –117.3 (s, 1F, CF), –73.4 (s, 3F, CF_3). IR (KBr): *v* 3238*m*, 3148*w*, 3063*m*, 1726*m*, 1616*w*, 1559*m*, 1518*m*, 1416*w*, 1362*m*, 1304*w*, 1249*w*, 1208*m*, 1191*m*, 1170*m*, 1126*w*, 1097*w*, 918*w*, 830*w*, 803*w*, 743*w*, 691*w* cm^{-1}. ESI-(+)-MS: *m/z* 282 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 280 (100%, $[M–1]^-$). HR-EI-MS: calcd. for $C_9H_7F_4N_3OS^+$ (M^+): *m/z* 281.02460; found: *m/z* 281.02429.

4.5.9. N-*(4-Methoxyphenyl) trifluoroacetic acid thiosemicarbazide* (**6i**). Yield: 401 mg (68%), colorless crystals, m.p. = 140–141 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.77 (s, 3H, CH_3), 6.93–6.94 (m, 2 arom. CH), 7.26–7.27 (m, 2 arom. CH), 9.73 (br. s, 1H, NH), 9.88 (br. s, 1H, NH), 11.47 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 55.7 (OCH_3), 114.0, 132.1 (4 arom. CH) 127.8 (1 arom. C–NH), 116.4 (q, $^{2}J_{C,F}$ = 286.5 Hz, CF_3), 156.8 (q, $^{2}J_{C,F}$ = 35.7 Hz, CF_3**C**=O), 157.5 (1 arom. C–OCH_3), 181.9 (C=S). ^{19}F NMR (565 MHz, DMSO-d_6): δ –73.6 (s, 3F, CF_3). IR (KBr): *v* 3424*w*, 3214*m*, 3046*w*, 2966*w*, 2943*w*, 2918*w*, 2845*w*, 1716*m*, 1613*w*, 1589*w*, 1545*m*, 1516*m*, 1469*w*, 1357*m*, 1302*w*, 1240*m*, 1215*m*, 1187*m*, 1168*m*, 1130*w*, 1101*w*, 1028*m*, 925*m*, 841*w*, 783*w*, 742*w*, 688*w*, 658*w* cm^{-1}. ESI-(+)-MS: *m/z* 294 (100%, $[M+1]^+$), ESI-(–)-MS: *m/z* 292 (100%, $[M–1]^-$). HR-EI-MS: calcd. for $C_{10}H_{10}F_3N_3OS^+$ (M^+): *m/z* 293.04458; found: *m/z* 293.04374.

4.5.10. N-*Phenyl difluoroacetic acid thiosemicarbazide* (**6j**). Yield*:* 394 mg (80%), colorless crystals, m.p. = 143–144 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.30 (t, $^{2}J_{C,F}$ = 50.8 Hz, CHF_2), 7.19–7.43 (m, 5 arom. CH), 9.79 (br. m, 2H, 2 NH), 10.91 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ. 108.6 (t, $^{1}J_{C,F}$ = 244.8 Hz, CHF_2), 125.8 (1 arom. C–NH), 128.7, 139.4 (5 arom. CH), 162.3 (t, $^{2}J_{C,F}$= 25.0 Hz, CHF_2**C**=O), 181.4 (C=S). ^{19}F NMR (565 MHz, DMSO-d_6): δ –126.9 (d, $^{2}J_{F,H}$ = 50.8 Hz, 2F, CHF_2). IR (KBr): *v* 3284*m*, 3163*m*, 3033*m*, 2886*w*, 1725*s*, 1592*w*, 1523*s*, 1500*s*, 1452*m*, 1374*w*, 1335*w*, 1290*w*, 1241*w*, 1201*m*, 1150*s*, 1120*m*, 1090*s*, 1027*w*, 1004*w*, 970*w*, 935*w*, 911*w*, 820*w*, 742*m*, 697*s*, 668*w*, 636*w*, 616*w* cm^{-1}. ESI-(+)-MS: *m/z* 246 (50%, $[M+1]^+$), 268 (100%, $[M+23]^+$). HR-EI-MS: calcd. for $C_9H_9F_2N_3OS^+$ (M^+): *m/z* 245.04344; found: *m/z* 245.03121.

4.6. Cyclization of thiosemicarbazides ***6g–j*** *to 1,3,4-oxadiazoles* ***7a–d***

Method A – General procedure. Dicyclohexylcarbodiimide (DCC, 305 mg, 1.48 mmol) was added to a solution of the appropriate thiosemicarbazide (**6g–j**) (1.0 mmol) in anhydrous THF (~15 ml). The mixture was heated at reflux for 9 h and then the solvent was evaporated. The obtained crude products were purified by column chromatography (SiO_2, hexane/Et_2O, 6:4).

Method B – General procedure. Tosyl chloride (229 mg, 1.20 mmol) and Et_3N (2.20 mmol, 222 mg) were added to a solution of thiosemicarbazide **7g** (263 mg, 1.0 mmol) in *N*-methylpyrrolidin-2-one (NMP, 8 ml). The mixture was stirred for 3 h at room temperature and after this time, H_2O (~10 ml) and CH_2Cl_2 (15 ml) were added. The organic layer was separated and the aqueous layer was washed two times with dichloromethane (2×15 ml). The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. Next, the solvent was evaporated and the product was purified by column chromatography (SiO_2, hexane/Et_2O 6:4).

4.6.1. 2-Phenylamino-5-trifluoromethyl-1,3,4-oxadiazole (**7a**). Yield: 210 mg (92 %) method A; 140 mg (61%) method B; colorless crystals, m.p. = 129–131 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.08–7.10 (m, 1 arom. CH), 7.4–7.42 (m, 2 arom. CH), 7.6–7.7 (m, 2 arom. CH), 11.1 (br. s, 1H, NH) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ 116.8 (q, $^1J_{C,\,F}$= 268.1 Hz, CF_3), 118.2, 123.4, 129.7 (5 arom. CH), 138.1 (C(5)), 147.9 (q, $^2J_{C,F}$ = 42.9 Hz, **C**CF_3), 161.7 (C(2)NHPh). ^{19}F NMR (565 MHz, DMSO-d_6): δ –64.6 (s, 3F, CF_3). IR (KBr): *ν* 3186 *w*, 3082*w*, 2996*w*, 2944*w*, 2879*w*, 1676*s*, 1603*m*, 1588*m*, 1503*m*, 1407*w*, 1346*w*, 1333*w*, 1231*w*, 1210*m*, 1165*m*, 1142*m*, 1119*m*, 1058*w*, 1032*w*, 968*w*, 890*w*, 729*w*, 749*m*, 688*w*, 627*w* cm^{-1}. ESI-(+)-MS: m/z 230 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 228 (100%, $[M-1]^-$). HR-EI-MS: calcd. for $C_9H_6F_3N_3O^+$ (M^+): *m/z* 229.04630; found: *m/z* 229.04587.

4.6.2. 2-[(4-Fluorophenyl)amino]-5-trifluoromethyl-1,3,4-oxadiazole (**7b**). Yield: 219 mg (95%) method A; colorless crystals, m.p. = 147–149 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.24–7.27 (m, 2 arom. CH), 7.58–7.61 (m, 2 arom. CH), 11.11 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 116.8 (q, $^1J_{C,\,F}$= 268.0 Hz, CF_3), 116.2, 116.3, 119.8, 119.9 (4 arom. CH), 134.5 (C(5)), 147.9 (q, $^2J_{C,F}$ = 43.0 Hz, **C**CF_3), 158.4 (d, $^1J_{C,\,F}$= 238.0 Hz, 1 arom. C–F), 161.7 (**C**(2)NHC_6H_4F). ^{19}F NMR (565 MHz, DMSO-d_6): δ –120.2 (s, 1F, CF), –64.5 (s, 3F, CF_3). IR (KBr): *ν* 3337*w*, 3191*w*, 3074*w*, 2998*w*, 2945*w*, 2874*w*, 1679*s*, 1668*s*, 1607*m*, 1596*m*, 1511*vs*, 1441*w*, 1387*m*, 1328*m*, 1232*s*,

1164*m*, 1116*s*, 1057*m*, 968*w*, 830*m*, 750*m* cm^{-1}. ESI-(+)-MS: *m/z* 248 (100%, $[M+1]^+$). HR-EI-MS: calcd. for $C_9H_5F_4N_3O^+$ (M^+): *m/z* 247.03687; found: *m/z* 247.03693.

4.6.3. 2-[(4-Methoxyphenyl)amino]-5-trifluoromethyl-1,3,4-oxadiazole (**7c**). Yield*:* 193 mg (80%) method A; colorless crystals, m.p. 153–154 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.75 (s, 3H, OCH_3), 6.98–6.99 (m, 2 arom. CH), 7.48–7.49 (m 2 arom. CH), 10.85 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 55.7 (OCH_3), 114.9, 119.9 (4 arom. CH), 116.8 (q, $^1J_{C,\ F}$= 267.9 Hz, CF_3), 131.2 (C(5)), 147.6 (q, $^2J_{C,F}$ = 42.7 Hz, **C**CF_3), 155.7 (1 arom. **C**–OCH_3), 162.0 (**C**(2)$NHC_6H_4OCH_3$). ^{19}F NMR (565 MHz, DMSO-d_6): δ –64.5 (s, 3F, CF_3). IR (KBr): *ν* 3281*m*, 3131*w*, 3061*w*, 3008*w*, 2954*w*, 2920*w*, 2836*w*, 1632*vs*, 1586*s*, 1540*m*, 1518*s*, 1457*m*, 1426*m*, 1383*s*, 1229*s*, 1171*s*, 1133*s*, 1060*m*, 1034*m*, 987*w*, 831*w* cm^{-1}. ESI-(+)- MS: *m/z* 260 (100%, $[M+1]^+$). HR-EI-MS: calcd. for $C_{10}H_8F_3N_3O_2^+$ (M^+): *m/z* 259.05686; found: *m/z* 259.05641.

4.6.4. 2-Phenylamino-5-difluoromethyl-1,3,4-oxadiazole (**7d**). Yield: 160 mg (82%), method A; colorless crystals, m.p. 157–158 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.07 (t, $^2J_{H,F}$ = 7.2 Hz 1H, CHF_2), 7.38–7.40 (m, 3 arom. CH), 7.57–7.59 (m, 2 arom. CH), 10.87 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 107.1 (t, $^1J_{C,\ F}$= 235.2 Hz, CHF_2), 117.9, 123.0, 129.6 (5 arom. CH), 138.5 (C(5)), 153.2 (t, $^2J_{C,F}$ = 28.6 Hz, **C**CHF_2), 161.7 (C(2)NHPh). ^{19}F NMR (565 MHz, DMSO-d_6): δ–119.9 (d, $^2J_{F,H}$ = 51.4 Hz, 2F, CHF_2). IR (KBr): *ν* 3329*w*, 3252*w*, 3189*w*, 3073*w*, 3023*m*, 2955*m*, 2882*m*, 2748*w*, 2660*w*, 1668*s*, 1602*s*, 1589*s*, 1504*s*, 1479*m*, 1394*w*, 1375*m*, 1355*m*, 1292*m*, 1230*w*, 1108*m*, 1050*s*, 987*m*, 885*w*, 838*m*, 748*s*, 730*m*, 686*m* cm^{-1}. ESI-(+)-MS: m/z 274 (100%, $[M+23]^+$); ESI-(–)-MS: *m/z* 250 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_7F_2N_3O^+$ (M^+): *m/z* 211.05572; found: *m/z* 211.05605.

*4.7. Cyclization of thiosemicarbazides **6g**,**i** to 1,2,4-triazole-3-thiones **8a**,**b** – General procedure*

An aqueous solution of NaOH (2%, ~2 ml) and an appropriate thiosemicarbazide (**6g**,**i**) was heated at reflux for 3 h. Next, the reaction mixture was neutralized with acetic acid, the product was extracted with AcOEt (3×25ml), and the combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude products were purified by column chromatograpy (SiO_2, hexane/AcOEt 6:4).

*4.7.1. 2,4-Dihydro-4-phenyl-5-trifluoromethyl-3*H*-1,2,4-triazole-3-thione* (**8a**) [15]. Yield: 42 mg (34%), pale-yellow crystals, m.p. = 170–172 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.50–7.51 (m, 2 arom. CH), 7.59–7.60 (m, 3 arom. CH), 14.69 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 117.1 (q, $^{1}J_{C,F}$= 269.1 Hz, CF_3), 128.9, 129.9, 130.8 (4 arom. CH), 132.9 (1 arom. C), 140.7 (q, $^{2}J_{C,F}$ = 39.9 Hz, **C**CF_3), 171.3 (C=S). ^{19}F NMR (565 MHz, DMSO-d_6): δ – 62.7 (s, 3F, CF_3). IR (KBr): *v* 3145*m*, 3091*m*, 3033*m*, 2911*m*, 2853*m*, 2741*m*, 1597*m*, 1498*s*, 1474*s*, 1446*s*, 1458*s*, 1344*w*, 1277*s*, 1238*s*, 1219*s*, 1176*s*, 1149*s*, 1093*m*, 1036*m*, 984*m*, 775*m* cm^{-1}. ESI-(+)-MS: *m/z* 246 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 244 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_6F_3N_3S^+$ (M^+): *m/z* 245.02345; found: *m/z* 245.02339.

*4.7.2. 5-Difluoromethyl-2,4-dihydro-4-phenyl-3*H*-1,2,4-triazole-3-thione* (**8b**) [15]. Yield: 41 mg (36%), colorless crystals, m.p. = 187–189 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.04 (t, $^{2}J_{H,F}$ = 51.6 Hz, 1H, CHF_2), 7.46–7.47 (m, 2 arom. CH), 7.57–7.62 (m 3 arom. CH), 14.41 (br. s, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ 107.8 (t, $^{1}J_{C,F}$ = 235.9 Hz, CHF_2), 128.7, 129.8, 130.4 (5 arom. CH), 133.3 (1 arom. C), 144.9 (t, $^{2}J_{C,F}$ = 27.9 Hz CHF_2**C**), 170.5 (C=S). ^{19}F NMR (565 MHz, DMSO-d_6): δ –119.2 (d, $^{2}J_{F,H}$ = 50.8 Hz, 2F, CHF_2). IR (KBr): *v* 3249*w*, 3149*w*, 3089*m*, 3037*m*, 2999*w*, 2902*m*, 2848*m*, 2745*m*, 1594*w*, 1541*m*, 1497*s*, 1487*s*, 1435*m*, 1340*w*, 1323*m*, 1270*s*, 1229*m*, 1193*w*, 1176*w*, 1126*m*, 1077*s*, 1056*s*, 1015*w*, 823*m*, 776*m*, 738*w*, 724*w*, 690*m* cm^{-1}. ESI-(+)-MS: *m/z* 228 (100%, $[M+1]^+$); ESI-(–)-MS: *m/z* 226 (100%, $[M–1]^–$). HR-EI-MS: calcd. for $C_9H_7F_2N_3S^+$ (M^+): *m/z* 227.03287; found: *m/z* 227.03285.

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